Conclusive Evidence for a Retention−Retention Pathway for the Molybdenum-Catalyzed Asymmetric Alkylation

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Metal-catalyzed asymmetric alkylation reactions are well-documented to proceed in two basic steps: oxidative addition of the allylic electrophile to the ligated metal to form an asymmetric π-allyl intermediate followed by nucleophilic displacement to afford the product. Both steps can proceed with either retention or inversion, or can be stereoindiscriminate. Extensive work on the Pd-catalyzed allylic alkylation has shown the overall stereochemistry is generally retention, with the two steps both proceeding with inversion.[1] For the Mo-catalyzed reaction, Trost has also shown the reaction proceeds with net retention,[2] but the stereochemistry of each step has not been definitively elucidated. While logical to assume the Mo-catalyzed reaction also proceeds by inversion−inversion, a few studies have shown that stoichiometric oxidative additions with Mo can occur with retention,[3−6] and Kočovský reported a Mo-catalyzed allylic alkylation of a constrained system that is best explained by a retention−retention mechanism.[7] As described herein, we report conclusive evidence that in noncon-strained systems the Mo-catalyzed allylic alkylation proceeds via a ret−ret pathway.

Malkov, Lloyd-Jones, and Kočovský have used labeled substrates **1a** and **2a** to probe the mechanism of the Mo-catalyzed allylic alkylation (Scheme 1) employing ligand **9**.[8] Although evidence for $\pi-\sigma-\pi$ equilibration was obtained and the reaction was shown to proceed with net retention, they were unable to distinguish between an overall inv−inv or ret−ret sequence.
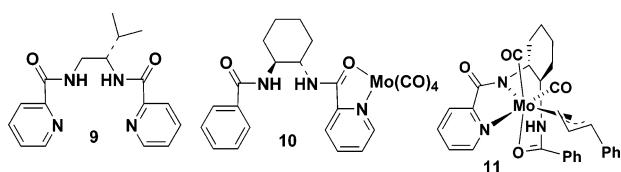
Recently, we reported the crystal structure of the π-allyl intermediate **11** formed in the Mo-catalyzed allylic alkylation using ligand complex **10**.[9] The structure revealed that one face of the π-allyl intermediate was clearly open for backside attack, yet reaction via this mode predicted a stereochemical outcome opposite to that observed experimentally. Thus, the nucleophilic addition must be occurring either via backside attack with an unobserved minor complex (Curtin−Hammett conditions) or via a retentive pathway involving the major diastereomer. As outlined below, the availability of the labeled substrates **1a** and **2a**, coupled with the crystal and solution structures of the π-allyl intermediate, have provided the tools to establish whether the Mo-catalyzed allylic alkylation proceeds via the inv−inv or ret−ret pathway.

The catalytic reactions of substrates **1a** and **2a** using Mo-ligand complex **10** afforded the same products as with ligand **9** (Scheme
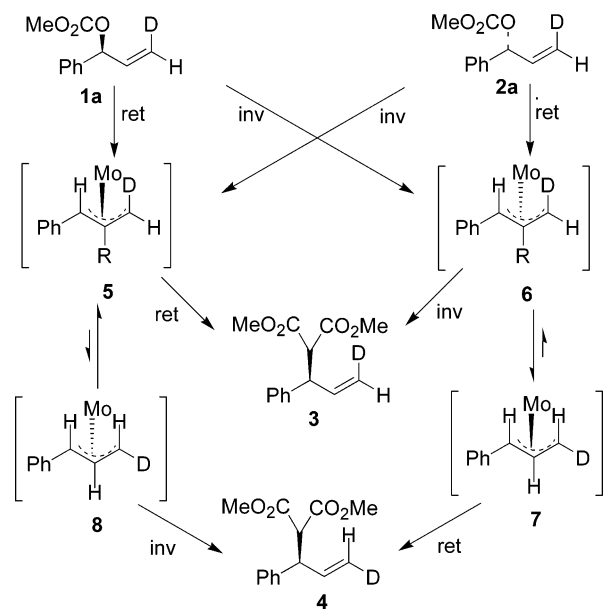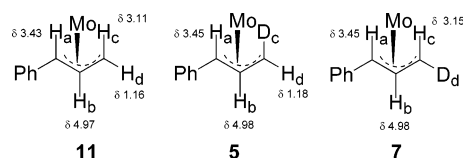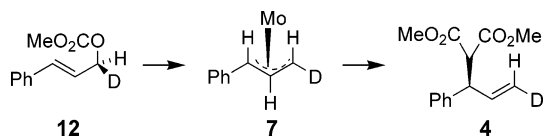
Scheme 1

Chart 1

1). Substrate **1a** provided product **3** with no transposition of the deuteron, while substrate **2a** resulted in formation of the *trans*-deuterated product **4**.

Stoichiometric reaction of substrate **1a** with **10** in THF in the absence of a nucleophile cleanly afforded the π-allyl intermediate. ^{1}H NMR examination of this complex, in comparison with the protio structure **11** (Chart 1), indicated the deuteron was at position "c" (structure **5**, Chart 1). Because the label has not been transposed, no $\pi-\sigma-\pi$ equilibration has occurred upon formation of the major isomer observed in solution. Based on solution phase nOe measure-ments of the protio complex, either π-allyl isomer **5** or **6** is possible.[10] However, the stereochemistry of the protio complex in the X-ray crystal structure corresponds to that shown in structure **5**, suggesting the major π-allyl complex is formed with retention of configuration and no $\pi-\sigma-\pi$ equilibration. Addition of sto-ichiometric sodium dimethyl malonate (in the presence of 1 equiv of $Mo(CO)_6$)[9] converted the π-allyl intermediate to product **3** with no transposition of the deuteron. This confirms the reaction is occurring via a retention−retention pathway, **1** to **5** to **3** (Scheme 1). [11]
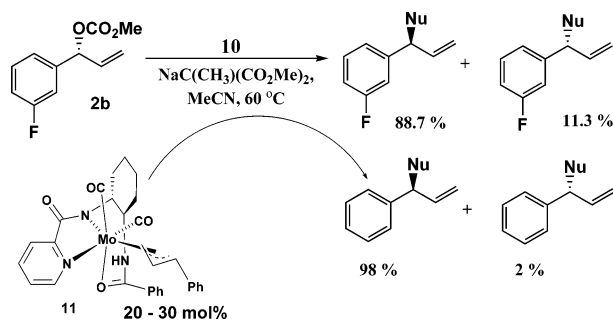
Scheme 2

Scheme 3

Similarly, solution NMR analysis of the complex derived from **2a** indicated the deuteron was at position "d" (structure **7**, Chart 1) resulting from transposition of the label. Based on a comparison with the X-ray crystal structure of the protio complex, the stereochemistry of the π-allyl intermediate was that corresponding to structure **7**. In this case, formation of the π-allyl complex occurred with retention to produce the unobserved intermediate **6**, which was rapidly converted to the observed **7** via π−σ−π equilibration. Addition of sodium dimethyl malonate converted the π-allyl intermediate **7** to product **4**, so the π-allyl intermediate observed in solution afforded product with retention and no transposition of the label.

Next, catalytic and stoichiometric reactions were carried out with deuterated linear carbonate **12** (Scheme 2). The major π-allyl complex observed by ^{1}H NMR was structure **7**, indicating Mo added from the same side as the leaving group. Stoichiometric addition of sodium dimethyl malonate converted the π-allyl complex to product with retention of stereochemistry and no transposition of the deuteron. The catalytic reaction proceeded with similar results.

An assumption in the preceding analysis is that the major π-allyl complex observed in solution is that which crystallizes. Conceivably, the X-ray structure of the protio complex could be that of the minor isomer, because minor and major species are in equilibrium in solution. To address this possibility, competition experiments were carried out with the 3-F substrate **2b** and π-allyl complex **11** (Scheme 3). Reaction of **2b** with catalyst complex **10** represents the mismatched case wherein the minor diastereomer of the π-allyl complex (cf., **6**) is kinetically generated and must equilibrate to the major complex (cf., **7**) prior to nucleophilic attack. The reactions were carried out with sodium dimethyl methylmalonate in MeCN, conditions which produce a substantial memory effect[12] such that the ee for the reaction with both **2a** and **2b** is 74%. The experiments were conducted as follows: the catalytic reaction of the 3-F substrate **2b** was initiated, and then complex **11** (20−30 mol %) derived from the unsubstituted analogue was added after the reaction was smoothly turning over (15−45% conversion). If the isolated

complex **11** was in fact the minor isomer, and required equilibration to the major isomer prior to reaction with the nucleophile, then both the 3-F and the unsubstituted products should exhibit a memory effect and have similar, low ee's. If the isolated complex **11** is the major complex, and does not require equilibration, then a high ee should result, similar to that observed with **1a**. The results of two experiments confirmed the latter case: the ee for the 3-F product was 77.5 ± 1.5%, while that derived from complex **11** was 96%.

In conclusion, the X-ray and solution structures of the π-allyl complex, in conjunction with deuterium labeling studies and competition experiments, conclusively show the reactions of branched and linear substrates **1**, **2**, and **12** proceed via a ret−ret mechanism. We believe this is the first concrete evidence of a general metal-catalyzed allylic alkylation that proceeds via a ret−ret mechanism. Kinetic and theoretical studies are in progress to further probe the mechanism of this reaction.[13]

Supporting Information Available: Further details and procedures for the allylic alkylation reactions and competition experiments (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) Complex **5/6** can exist in any of four possible isomers wherein the ligand binds in a facial, tridentate fashion in one of two geometries (defined by either Δ or Λ stereochemistry between the skew lines formed by the two CO ligands and the two bound N atoms of the chiral ligand) and the π-allyl fragment binds via its *re* or *si* face.
(11) A reviewer has suggested that π-allyl complexes (i.e., **5** and **6**) could be equilibrating via Mo−Mo exchange and still be consistent with an inversion process. However, the stereospecific nature of the reaction, **1a** giving **3** and **2a** giving **4**, excludes Mo−Mo exchange (inv) as a significant pathway. See Supporting Information for further details.
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(13) Complexation of both substrate[3−6] and nucleophile may account for the retentive pathways of each step. As an alternative, Kočovský (Kočovský, P.; Malkov, A. V.; Vyskočil, S.; Lloyd-Jones, G. C. *Pure Appl. Chem.* **1999**, *71*, 1425−1433) has suggested the nucleophilic substitution step in Mo-catalyzed alkylations may be occurring via an η^1 complex with the nucleophile attacking in an S_N2' mode. Because the π−σ−π equilibration occurs via the η^1 complex, it is clearly an accessible intermediate, but is not consistent with memory effects observed in these reactions because the pathways of the matched and mismatched substrates would converge at this intermediate. An alternative would be a π−σ−η^3 intermediate.

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